X chromosome reactivation dynamics reveal stages of reprogramming to pluripotency.

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Public Summary:
Our study shows how chemical modifications of DNA in cells controls the activity of entire chromosomes. In order to create induced pluripotent stem cells for disease therapies, we discovered that these chemical modifications must be removed in a sequential order along with the reactivation of embryonic stem cell genes.

Scientific Abstract:
Reprogramming to iPSCs resets the epigenome of somatic cells, including the reversal of X chromosome inactivation. We sought to gain insight into the steps underlying the reprogramming process by examining the means by which reprogramming leads to X chromosome reactivation (XCR). Analyzing single cells in situ, we found that hallmarks of the inactive X (Xi) change sequentially, providing a direct readout of reprogramming progression. Several epigenetic changes on the Xi occur in the inverse order of developmental X inactivation, whereas others are uncoupled from this sequence. Among the latter, DNA methylation has an extraordinary long persistence on the Xi during reprogramming, and, like Xist expression, is erased only after pluripotency genes are activated. Mechanistically, XCR requires both DNA demethylation and Xist silencing, ensuring that only cells undergoing faithful reprogramming initiate XCR. Our study defines the epigenetic state of multiple sequential reprogramming intermediates and establishes a paradigm for studying cell fate transitions during reprogramming.